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VOLUME 11 SEP 18 1953 NUMBER 9

NUTRITION REVIEWS

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SEP 23 1953
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September 1953

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Published Monthly by

THE NUTRITION FOUNDATION, INC.

CHRYSLER BUILDING NEW YORK 17, N. Y.

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ERRATA

(Series of reports from the Office of the Quartermaster, Environmental Protection Branch) Vol. 11, p. 229, col. 1, last line, and col. 2, paragraph 3, line 6: Munroe *should read* Munro; col. 2, line 1, Report No. 186 *should read* Report No. 184.

NUTRITION REVIEWS

VOL. 11 SEPTEMBER 1953 No. 9

RECOLLECTIONS OF THE "BERIBERI-PREVENTING SUBSTANCE"

The death of Colonel E. B. Vedder, U. S. Army Medical Corps, on January 30, 1951, has recalled to memory many incidents of the early history of the study of what we now call thiamine. It was early in September 1910 that Colonel Vedder called on me in Manila with a half-liter bottle of rice polish extract under his arm. He had first seen my chief who doubtless chose me as the greenest and the least busy member of his staff.

Vedder reviewed for me the work of Takaki, Schaumann, Eijkman and especially that of Fraser and Stanton who had then just reported their classic experiment in which they induced beriberi with white rice in Javanese laborers in Malaya and prevented it with parboiled rice in a control camp. He also told me of his own work. Using chickens he had demonstrated that polyneuritis could be prevented with rice polish extracts and that the preventive substance is diffusible through a collodion membrane and is adsorbed on animal charcoal. He had also tried rice polish extract in the treatment of human beriberi and had had some success with infants. He wanted my help in "analysis" of the extract for all components. He also proposed a little later that I should undertake the systematic manufacture of a standardized rice polish extract for distribution through public health centers for treatment of infantile beriberi.

Naturally, flattered by an opportunity to work on such a basic problem, I applied myself vigorously to it, exhibiting more zeal than skill. At the time the cause of beriberi was still very controversial. Many experienced physicians still held the view that it was infectious in nature. A few held that it was due to spoiled rice; some that a toxin analogous to ergot was responsible; some that a deficiency of phosphorus produced it. A favorite counter argument to the views of Eijkman was that polyneuritis gallinarum is not beriberi. Few indeed conceded that the infantile disease "taon" could have any relation to beriberi. Manila's infant mortality was then approximately 500 per 1000 live births, and the subject was in lively dispute.

It was at this juncture that a young American physician, Vernon Andrews, determined on a direct approach. He induced 4 women who had recently lost their babies from taon to nurse young puppies at their breasts. Within four to six weeks all 7 puppies died with symptoms and necropsy findings resembling those of taon. It is amusing to recall that one woman objected to nursing a puppy whose eyes were still closed. "To overcome this difficulty," Andrews reports, "I had to give a puppy to her that was fourteen days old, and this fact may have had an influence on the effect produced in the puppy."

Andrews' experiment produced a profound impression which was further strengthened by the generally favorable responses in babies to therapy with rice polish extract prepared by Vedder and myself. Responses of adults were often much less favorable; mild cases of long standing generally showed only slight or very gradual improvement. We hatched various theories to account for this, but it seems in retrospect most probable that in the latter cases we were dealing largely with long-standing damage of an almost irreparable nature. Infantile cases were always acute. If untreated, death usually ensued in twenty-four to seventy-two hours after the mother first noted symptoms.

From time to time, however, we encountered adult cases of an acute type, more frequently with the copious edema of wet beriberi. These often responded as the babies

did. Probably Vedder, with the greater discernment of an experienced practitioner, was less discouraged by our failures than was I. For myself, I am frank to say that I fear I should have given up had we not had the occasional thrilling experience of dramatic responses from time to time.

For two years or so I clung to Vedder's apron strings, but when he was called home at the end of his regular tour of duty I cultivated friends among the doctors and health inspectors of the city. They would report beriberi cases to me and I would go out with my latest improved concentrate to try it out. Two cases stand out most vividly in my memory. One was a boy 10 or 12 years of age in the Philippine General Hospital. When I first saw him about noon he had been unconscious for some hours. The priest had said the last rites and his parents were in the room awaiting the end. As it happened I had an extract which I had just tested for several weeks on chickens and I thought it exceptionally potent. Blandly I reassured the parents and directed the doctor in the injection. About 5 o'clock I came back to see my patient. As I tiptoed into the doorway he raised himself on his elbow and said that he was very hungry.

Another time I attended alone a very youthful little mother in a nipa shack whose tiny blue-faced baby was dying in her arms. With a teaspoon I fed it some 2 or 3 cc. of the best concentrate I had and sat down beside the mother on the split bamboo floor to await results. Soon the breathing became quieter, the aphonic crying diminished. Within three hours the infant nuzzled at its mother's breast, nursed hungrily and fell into quiet sleep.

I often berate myself for having failed to keep track of these two people.

Beriberi has now diminished in fatality in Manila, deaths falling from 577 per 100,000 in 1910 to 14 in 1950. Much of this is due to the use of rice polish extract; more perhaps to synthetic thiamine. However, in the provinces, except in Bataan and Tarlac where enriched rice has been introduced, beriberi mortality still holds high rank. In fact, the reported deaths are now often higher than in those earlier years when the disease was less well recognized. Delay of a generation's duration in the application of new knowledge can still ensue when change of custom or a small economic outlay are involved for every family.

While the work of my Manila years had enjoyed the security of a regular, if small, government salary, this was not the case when I returned to the United States in 1915, in keeping with the progressive Filipinization of the Philippine government service. Vitamins had then no recognized place in the food problems of our country. For twenty years thereafter I was forced to fit the beriberi problem into the interludes of other jobs which were necessary to support my growing family. Thanks to the forbearance of my superiors, first in Federal government service, later in the Bell Telephone system, I was able, with the later aid of research grants, chiefly from Fleischmann and from Carnegie Corporation, to carry on the earlier work which I could not dismiss from mind.

For four years this work was sandwiched in with assigned government tasks, chiefly war jobs. Here I worked often with Atherton Seidell who introduced the use of fuller's earth (acid clays) as an adsorbent. This proved a key reagent in the ultimate isolation process, first of Jansen and Donath in 1926, and of our later better procedure in 1934. For seven years various fractionation procedures were explored in a home basement laboratory in New Jersey. Then, as Carnegie money and Columbia facilities came to my aid, a more intensive attack was possible in company with Robert Waterman who had volunteered as an out-of-hours assistant and intellectual sparring partner. In some added leisure provided by the industrial depression we finally obtained the crystalline substance in gram quantities.

A good notion of structure was soon pro-

vided by the fortunate sulfite cleavage reaction. By the time the details of structure were ferreted out in borrowed space and with facilities of Merck & Co., Inc., a synthesis was at hand. This, as further perfected by Merck, has since produced hundreds of tons of thiamine. Much of this production has been used to enrich flour, bread, and later corn and rice. The patents, assigned outright to Research Corporation, have so far produced nearly $3,500,000 for the Williams-Waterman Fund for the Combat of Dietary Diseases. Half of this has been spent for research and demonstrations in nutrition; half remains for further efforts.

ROBERT R. WILLIAMS, *Chairman,*
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ADULT STANDARDS OF BODY WEIGHT OUTSIDE THE UNITED STATES

In Great Britain a large mass of data on body weight at different ages and heights was obtained in the course of inquiries carried out between 1943 and 1949 by the Ministry of Food. The purpose of the surveys was to provide a biologic check on the adequacy of national food supply. Only gross changes in weight were looked for, and none was found. There was an average rise of about 2 pounds in men and 3 pounds in women between 1943 and 1945, with a subsequent small decrement of about 1 and 0.5 pounds in 1947, followed by a rise of 2 pounds in men and slightly more in women. In all three phases the average changes in body weight paralleled fairly closely the changes in the estimated energy value of the foods available for consumption, indicating an increment of about 140 calories, a decrease of 120 calories, and an increase of 120 calories per head per day, respectively, in the three periods (J. M. Harries and D. F. Hollingsworth, *Brit. Med. J.* **1,** *75* (*1953*)).

The data on height and weight, collected in 1943, were analyzed in detail by W. F. F. Kemsley (*Ann. Eugenics* **15,** *161* (*1950*); **16,** *316* (*1952*)). The 1952 publication contains tables of mean weights for nineteen age groups, covering the age range 14.5 to 79.5 years, as well as the value of weight at the first, fifth, ninety-fifth, and ninety-ninth centile for five heights. The information on the distribution of the weights is a valuable feature of Kemsley's presentation, lacking in the traditional height-weight standards. The distributions of weights at a given height are skewed, the deviations above the mean being greater than those below the mean. Consequently, standard deviations cannot be used to describe such distributions and must be replaced by selected centile values.

The means, given in the standard height-weight tables, conceal the very considerable variations existing between individuals of the same age and height. Furthermore, and this is a very crucial point, the increments in weight with age are not identical for light, medium and heavy individuals. In particular, the lowest centiles were changed much less during maturity while mean weights showed substantial gains. The first centiles of males at 67 inches and ages of 20 and 50 corresponded to 110 and 116 pounds, the smoothed means to 137 and 148 pounds, the ninety-ninth centiles to 173 and 202 pounds, yielding differences of 6, 11, and 29 pounds, or 5.5, 8.0, and 16.8 per cent.

Kemsley's data cover also the higher age groups, whereas the generally used American tables end at the age of 55 years. Both males and females show a decrement in height and weight in the upper age range. Interestingly enough, in men the mean weights *at a given height* do not show a decrement even in the seventh decade while women indicate a loss of 4 to 5 pounds.

It has been noted that following 1943 there

was in England a substantial average increase in body weight (a total of about 3 pounds in men, 6 pounds in women). This means that Kemsley's painstaking labor will have to be repeated when the weight picture becomes stabilized. In view of the medical dangers of overweight, well documented by the insurance statistics, one must differentiate between an accurate description of the weight of a population, as reflected in the means, and the biologically desirable values of body weight. The reviewer is not aware of British data which would provide a medical evaluation of the observed rise in national weight. Also, it should be pointed out that the size of the sample used in the study of average weight changes between 1943 and 1949 was not very large (3000 to 4500 individuals) and the presence of the trend may need confirmation based on a larger and more representative sample.

Standards of growth for young people (14 to 21 years of age) working in industry in Great Britain were provided by E. J. Boothby, M. A. Guy, and T. A. L. Davies (*Monthly Bull. Ministry of Health* **11,** *208 (1952)*). In addition to height and weight, skin thickness was measured below the right scapula by special calipers and the maximum distance between the epicondyles of the left humerus was determined. Also, volume measurements were attempted by weighing the water which overflowed as the subjects were immersed, except for nose and mouth, in a tank of warm water. They lay in the water, with the neck supported by the hand of an experimenter, breathing quietly. In view of the large error of measurement involved in such a procedure and absence of information on the amount of air in the lungs at the time of inspiration, the data are of limited use. No comparison of mean "density" values for boys and girls of a given age was attempted, and age trends were not examined.

For girls 15 to 18 years of age the mean skin thickness was 0.7 cm., for boys in this age group it was 0.5 cm., confirming the sex differences in fatness. The respective values of epicondylar width were 5.9 and 6.9 cm., respectively. Of some interest is the consideration of differences in weight and volume of girls differing in physical maturity as measured in terms of menarche. For those who had menstruated for one year, as compared with nonmenstruating girls, the difference is 7.5 kg. of weight, and about 8.3 liters in volume. This is only an approximative value, at the best, and should be corrected for the density of water at the temperature in the tank, which was certainly less than 1. It is apparent, nevertheless, that the tissues gained are of low density, *i.e.*, must have included a fair amount of fat.

Of interest is the author's scheme for classifying human physiques using underweight-overweight (based on height-weight relationship) as one and skin thickness as the other "dimension." This yields the central group (average in reference to both weight and fatness), four groups average in one but deviating in the other characteristic, and four extreme groups (heavy and fat, heavy and lean, light and fat, and light and lean). An active but obese individual, a football player in training, an obese and inactive person, and the typical undernourished individual would fit these four extreme categories. The present scheme does not differentiate between the contribution of the muscles and the bones to the gross body weight. This would require a tridimensional scheme.

While the weight standards in many parts of the western world are not very satisfactory, in some parts of the world no reference data whatsoever are available. For this reason, as well as because of a more than usually thorough coverage of ages and anthropometric criteria, the study by K.-P. Chen *et al.* (*Mem. Fac. Med., Nat. Taiwan Univ.* **1,** *168 (1951)*) on the physical development of the natives of Botel Tobago Island is of interest. The island lies south of

Formosa and its inhabitants lead a primitive life. Unlike the case in many other groups, there was no increment in weight during maturity, with average body weights remaining essentially constant over a period of twenty-five years (53.2 kg. in men, 42.7 kg. in women at 25 years for height of 155 and 145 cm., respectively). In the age group 50 to 60 years there was an indication of decrement of body weight.

In addition to height and weight, the limb circumferences (upper arm, outstretched and bent, forearm, thigh and calf) as well as the chest circumference and the grip-strength of the right and left hand were measured. In order to complete the anthropometric evaluation of the nutritional status, information on subcutaneous fat and the size of the skeleton (from lateral diameters of the pelvis and of the bones of the extremities) would have been desirable. The physical growth of the Yami tribe was compared with several other races (Ami, Tayal, Taiwanese, Cantonese). The bibliographic references to weight and developmental standards would be useful to individuals planning nutritionally-oriented research in these parts of Asia.

The table of average heights and weights of the Japanese was revised recently in the context of studies on dietary allowances. The synopsis of the study by K. Yanagi *et al.* was included in the "Annual Report of the National Institute of Nutrition, Tokyo" (*pp. 1–3 (1951)*). In men the height reaches its maximum in the third decade of life (161.9 cm.), decreasing by about 1 cm. for each of the three subsequent decades and more rapidly beyond the age of 60. In women the average height in the third decade is 150.1 cm. and the decline in stature is much the same as in men. Body weight shows only a very small increase during maturity (in the third decade, 55.5 and 48.5 kg. for men and women, respectively; maximum of 56.7 and 50.0 kg. between the ages of 41 and 51; decline to 51.0 and 44.0 kg. in individuals 71 years old and older). This is in striking contrast to the United States where the medico-actuarial tables of 1912 indicate, in individuals of similar weight to the Japanese averages, increments of about 7.7 and 7.3 kg. between the ages of 25 and 55.

Thus the Japanese as a nation follow closely the principle of "ideal" weights, formulated by the statisticians of the Metropolitan Life Insurance Company (*Statist. Bull.* **23,** *No. 10, 6 (1942)*; **24,** *No. 6, 6 (1943)*), namely, that increase in body weight is a statistically "normal" but not necessarily desirable phenomenon. The weight increase during maturity was interpreted as largely reflecting the effect of persisting in the habit of consuming the same amount of food while physical activity decreases. It was suggested that for adults, irrespective of age, the most favorable weights for health and longevity are close to the averages observed at ages 25 to 30. Should the low incidence of degenerative diseases of the heart and blood vessels in Japan be regarded as an argument supporting such a thesis?

ABSORPTION AND METABOLISM IN NONTROPICAL SPRUE

Nontropical sprue, as the synonym "idiopathic steatorrhea" implies, is ordinarily considered to be primarily associated with malabsorption of fat, while other absorptive abnormalities are considered minor in degree or secondary to the steatorrhea. Such frequently observed metabolic aberrations as flat glucose tolerance curves, disturbed intestinal motility, anemia, hypoproteinemia, hypocalcemia, hypoprothrombinemia and vitamin deficiencies have been considered generally to be due to the results of the steatorrhea, or due to diarrhea associated with an irritated intestine. It has

also been suggested that sprue patients excrete normal or only slightly increased amounts of nitrogen in their feces and thereby can be differentiated from patients with insufficiency of the external pancreatic secretions.

Despite the information available concerning the metabolic changes mentioned, relatively little is known of the influence of this disease on the metabolism of such elements as sodium, chloride and potassium. In an attempt to determine more exactly the extent of the absorptive defect in nontropical sprue, M. W. Comfort, E. E. Wollaeger, A. B. Taylor, and M. H. Power (*Gastroenterology* **23,** *155 (1953)*) have reviewed data obtained from their studies of 11 cases of this disease. These data, compiled from one or more periods of metabolic study in each patient, have been compared with the findings in normal individuals studied in the same laboratory and with those gleaned from published reports of similar investigations.

The fecal solids, fat and nitrogen in a group of patients receiving diets containing 100 to 103 g. of fat and 18.5 to 19.2 g. of nitrogen were compared with measurements obtained in normal individuals receiving similar diets. Although patients with sprue varied widely in the degree of abnormality observed, the average of the group was 74.8 ± 7.3 g. of fecal solids daily in contrast to the upper limit of 42.2 g. in normal persons. In respect to fat and nitrogen the averages and ranges of sprue patients were 37.6 ± 5.0 g. and 3.5 ± 0.3 g. per day, which contrasted with 7.1 g. and 2.5 g. per day as the upper limits found in normal subjects.

This first group of patients with relatively high fat and nitrogen intake was also compared with a second group of patients ingesting 50 to 60 g. of fat and 11 to 14 g. of nitrogen and with a third group in which 45 to 54 g. of fat and 19 g. of nitrogen were ingested. The absolute amounts of fat lost in the feces of the individuals in these groups averaged less than those in the first group, although a greater percentage of ingested fat was lost in the feces. Fecal nitrogen, however, was greater both in absolute amount in the second and third groups and in terms of per cent of nitrogen taken in the diet. Regardless of the variations in intake of the three groups studied, the fecal findings were abnormal in nearly all instances. The magnitudes of the fat loss and nitrogen loss were not always proportionate in a given individual, however, and no constant correlation could be established between the fecal losses of these nutrients.

In another set of comparisons the findings in these patients were contrasted with those of patients suffering from chronic pancreatitis with steatorrhea. Low, average and high values of fecal solids, fecal fat, percentage of ingested fat found in the feces, fecal nitrogen and percentage of ingested nitrogen found in the feces were reported. In patients with sprue, the average and maximal values for solids, fat and percentage of ingested fat exceeded those in patients with pancreatic steatorrhea, but the lower ranges of excretion values were similar in the two diseases. The fecal nitrogen and percentage of ingested nitrogen found in the feces showed little difference at either the extremes or in the averages. The latter point is emphasized by the authors in view of the suggestion that these measurements could be used to differentiate the two conditions.

Also reviewed by the authors are their studies of the effect of intake upon fecal values. In one patient, raising the intake from 50 to 100 g. of fat doubled the fecal fat, while lowering the fat intake to 4.2 g. daily reduced the fecal fat to 14 g. In another patient, however, similar elevation of dietary fat resulted in an increase in the fecal fat from 14 g. to a level of 21 g., and the latter value fell as the disease appeared to improve spontaneously. Marked alterations in nitrogen intake were not followed by fecal nitrogen changes of the magnitude seen in

the case of fat. Attempts to determine the effect of dietary fat variation upon fecal nitrogen and of diet nitrogen variation upon fecal fat yielded inconclusive results. From these studies the authors suggest that the dietary fat intake is most influential in altering fecal loss when the disease is stable, while nitrogen intake is much less so.

Total nitrogen balances in these patients were usually positive except during acute exacerbations of the disease which were accompanied by marked increases in fecal nitrogen. This nitrogen retention is believed to reflect the pre-existing nitrogen deficit, but the authors also point out that in their patients nitrogen balance became negative when the absorbed nitrogen (amount fed minus the amount in the feces) fell to approximately 7 g. per day.

These workers have expended considerable effort in their analyses of calcium balances at various intakes and confirm previous reports of excessive calcium loss in the feces in this disease. Evidence is presented, however, to the effect that very high calcium intakes (2.6 g. daily) may overcome this loss. At lower intakes the calcium loss in the feces may exceed the amount ingested, thus implying that calcium secreted into the intestinal tract is not reabsorbed. The previously suggested causes of calcium loss are discussed and particular emphasis is placed upon the finding that these patients failed to demonstrate a consistent correlation between fecal fat and fecal calcium. This suggests that poor calcium absorption is not necessarily due to the formation of calcium soaps. In these studies, decreasing or increasing the fat intake and thereby changing the fecal fat loss did not significantly alter fecal calcium loss. The authors conclude that excessive fecal calcium excretion may be due to vitamin D deficiency or to malabsorption of calcium as one part of a widespread intestinal disturbance. Urinary calcium excretion was generally found to be low and showed only slight relation to the values for total or ionized serum calcium, although the urinary excretion was most markedly depressed when the total calcium was below 7 mg. per cent, or ionized calcium was below 3.5 mg. per cent.

Phosphorus balance was positive in all except one case in this series of patients, but the excretion of this ion in the feces exceeded its urinary excretion in 5 out of 8 patients. This finding is in contrast to the usual situation in normal persons and is interpreted as a possible reflection of excessive fecal calcium values, or of a specific malabsorption of phosphorus.

Although chloride, sodium and potassium studies were carried out in only 3 patients, excessive fecal loss of all three elements was observed in 2 patients, and in the third potassium excretion was excessive while chloride and sodium were within normal limits. In spite of these changes compensatory reduction in urinary excretion allowed positive sodium and chloride balances to occur. Potassium balance, however, revealed a net loss in 2 patients.

Exacerbation of the disease in one patient while under study enabled the authors to demonstrate the marked increase in fecal loss of all the nutrients which have been discussed above. With remission, these values returned toward pre-exacerbation levels and the authors express the opinion that the therapeutic measures used had little bearing upon this improvement. They contrast the alterations observed with those which they have reported during the administration of cortisone (A. B. Taylor, E. E. Wollaeger, M. W. Comfort, and M. H. Power, *Gastroenterology* **20,** *203 (1952)*; *Nutrition Reviews* **10,** *169 (1952)*). With use of this hormone rapid improvement in nearly all absorptive defects has been observed, but complete correction has not been possible.

These investigations yield impressive evidence that sprue includes a multitude of abnormalities, many of which appear to vary in severity independently of each

other. It is clear that the mechanisms which are disturbed may well be many, but the fact that clinical exacerbations appear to aggravate to a greater or lesser extent all of the absorptive disturbances, plus the fact that cortisone appears to correct many if not all of them, points to a possible common abnormality.

SERUM LIPIDS AND XANTHOMATOUS DISEASE

A variety of visible lipid deposits are well known in clinical medicine as the xanthomata. These vary from the prevalent limbal deposits known as arcus senilis through the circumorbital cutaneous deposits known as xanthelasma to the rarer and yet more dramatic intracutaneous and periarticular deposits of xanthoma tuberosum and finally to the nodules found attached to tendons and their sheaths known as xanthoma tendinosum. In addition there are certain well-known and distinct acute and localized dermatoses characterized by excessive lipid deposits and known as acute eruptive xanthomata.

An important and pressing question is the meaning of the appearance or presence of these lesions with respect to the patient's health. It has long been recognized that these lesions are associated more or less regularly with atherosclerosis. The various lesions have been classified empirically according to their appearance and the nature of the associated serum lipid disturbances. The introduction of the elegant methods of characterizing the serum lipoproteins with ultracentrifugal technics has permitted another exploration of the nature and meaningfulness of these xanthomatous diseases (J. W. Gofman *et al.*, *Science* **111,** *166 (1950)*).

N. N. Epstein, R. H. Rosenman, and J. W. Gofman (*Arch. Dermat. Syph.* **65,** *70 (1952)*) have examined the serum lipids of 35 subjects with the orbital skin lesions known as xanthelasma. It was observed that among these subjects, aged 40 to 63 years, there was a disproportionate number of individuals (47 per cent) with total serum cholesterol levels above 300 mg. per cent, a level which is widely acknowledged to be abnormal. Furthermore, the measurements of the remaining subjects were near this abnormal level. In contrast, the serum lipoproteins of the S_f 10 to 20 class were found in concentrations not significantly different from those of apparently well subjects. An important dissociation of these two serum lipid quantities was thus disclosed. The subjects of this study group as well as other groups of subjects with xanthelasma which have been studied were found to have more manifestations of atherosclerosis than would be expected in a group without xanthelasma.

This evidence suggests that the serum cholesterol levels may in fact be better criteria of the presence and progress of atherosclerosis than the levels of the S_f 10 to 20 class of lipoproteins. The authors' hypothesis that in time the hypercholesterolemia in these subjects will be followed by high levels of S_f 10 to 20 as the "lipid defect" becomes more severe, and that atherosclerosis will *then* develop does not appear tenable since clinical signs of atherosclerosis were already present in at least 20 per cent of the subjects. The authors point out the importance of a serial follow-up of this or a similar group of subjects in order to determine the true relation of these various measurements and cutaneous signs to one another.

Another study by J. McGinley, H. Jones, and J. Gofman (*J. Invest. Dermat.* **19,** *71 (1952)*) was concerned with similar serum lipid measurements in 14 subjects with either xanthoma tuberosum or xanthoma tendinosum, or with both of these manifestations. In these subjects the lipoprotein pattern obtained with the ultracentrifuge was abnormal in each instance

and the authors believe these patterns are sufficiently distinctive that the diseases may be differentiated by such means.

The subjects with xanthoma tuberosum showed the most deviated pattern and this was manifested especially by a large increase of the S_f 10 to 40 classes of lipoproteins. The authors believed that a positive correlation existed between the severity of the clinical lesions (considering the presence of coronary artery disease as well as the xanthomatous lesions) and the extent of the deviation of the lipoprotein pattern. However, there is as good evidence in the clinical data to conclude that the several clinical manifestations are age-dependent, for the less apparently diseased subjects were also generally the younger.

The 4 subjects with xanthoma tendinosum alone also showed the lowest S_f 10 to 20 levels and were said to show no defect in the higher lipoprotein classes. Five subjects with biliary cirrhosis associated with xanthoma were studied, and these showed a characteristic large increase of the S_f 6 to 8 classes and a great increase of the S_f 10 to 17 classes, but no increase in the lower density material above S_f 17. Three subjects with reticuloendothelial disease with abnormal lipid storage showed no abnormality of the serum lipoproteins.

A classification of the xanthomata is described which is based upon the ultracentrifugal characterization of serum lipoproteins. This grouping is unsatisfactory because it includes the xanthoma associated with diabetes, with pancreatitis and with idiopathic hyperlipemia, although no data are given to describe these diseases. The authors present data for 2 subjects with both tuberosum and tendinosum, 4 with tendinosum alone and 8 subjects with tuberosum alone. The variability of these quantities will require larger numbers of subjects before a definitive classification on this basis is acceptable.

The relation of these lipoprotein measurements to cholesterol measurements is of great practical importance. Although the authors summarily dismiss the cholesterol measurements as both without correlation with the S_f 10 to 20 measurement and without predictive value for the S_f 10 to 20 quantity, it must be remembered that a means to an end is sought here, namely, a measurement that will detect reliably, sensitively and efficiently the presence of atherosclerosis. Without exception the group studied with the xanthoma stigmata showed abnormally high cholesterol levels. It happens that they also showed abnormal elevations of certain serum lipoproteins. There is little to choose between the two laboratory measurements unless ease of accomplishment is considered, in which case the cholesterol measurement would be favored. Neither can such data reveal information concerning the relative "atherogenicity" of the several quantities until it can be established that a real difference in the extent of atherosclerosis exists between the tuberosum and tendinosum type of xanthoma for which the authors have demonstrated certain characteristic differences in the lipoprotein pattern. The dissociation of these two quantities observed by Epstein and coworkers in the subjects with xanthelasma would appear more applicable to this purpose. In the meantime the authors' proposal that the S_f 10 to 40 classes of lipoproteins are responsible for the atherosclerosis which results, whether in human subjects or experimental animals, must be considered unproved.

METABOLIC RATE AND THYROID FUNCTION FOLLOWING BURNS

Malnutrition is a frequent and serious complication in patients with severe burns. Disturbances in the metabolism of all nutrients so far studied are seen. Many of

the changes are similar to those observed following other types of injury and illness. Most of the reported studies have dealt with the problem of protein metabolism. In addition to the loss of nitrogenous compounds from the burned area, there is an increased urinary excretion of nonprotein nitrogen beginning three or four days after burns, reaching a peak during the first or second week and persisting for three or four weeks. The intensity of this reaction depends on the severity of the injury and the status (age, sex, nutrition, etc.) of the individual at the time of injury. The greatest losses of nitrogen are shown by the severely burned, previously well-nourished young adult male.

Although this phenomenon of increased urinary excretion of nitrogen following injury has been long recognized, its pathogenesis has not yet been established. Some of the factors which have been considered in this regard are (1) autolysis and absorption of tissue breakdown products, (2) inactivity, (3) specific amino acid deficiency, (4) renal dysfunction, (5) increased proteolytic enzyme activity, (6) reduced dietary intake, (7) increased metabolic rate, and (8) imbalance of endocrine activity (*Nutrition Reviews* **3,** *40, 86, 253 (1945)*; **4,** *6 (1946)*; **5,** *46 (1947)*; **6,** *20, 161 (1948)*; **7,** *123 (1949)*; **8,** *137 (1950)*; **9,** *257 (1951)*; **10,** *99, 195 (1952)*).

The majority of studies of endocrine activity following injury have been concerned with the adrenals. There is ample evidence to indicate an increase in adrenal activity following injury—for example, there is an early increased urinary excretion of 17-ketosteroids followed by an increased excretion of 11-oxysteroids. However, the increased adrenal activity may not be responsible for the increased urinary excretion of nitrogen, but, rather, the adrenal may act in a permissive fashion, that is, a certain level, but not necessarily increased level, of adrenal activity is necessary for the reaction to occur. Thus, adrenalectomized rats on a fixed maintenance dose of adrenal cortical extract will exhibit an increase in urinary nitrogen excretion after injury. It has been suggested that the adrenal may act primarily on carbohydrate metabolism and that the effects on protein metabolism are secondary.

The increased urinary nitrogen excretion may be consequent to a relatively decreased dietary intake in the face of an increased metabolic rate. Few data have been available regarding total oxygen consumption by the burned patient. Superficial and scanty observations have suggested that the metabolic rate is increased, but quantitative information as to the extent, duration, etc., of the elevation has not been at hand. Nor has it been known whether the apparent increase in metabolic rate is a result of increased thyroid activity. Accordingly, O. Cope *et al.* (*Ann. Surg.* **137,** *165 (1953)*) have followed thyroid function and oxygen consumption of patients with burns. A total of 15 patients with burns were studied. Twelve had extensive burns involving from 20 to 68 per cent of their body surfaces. It is stated that many of the burned areas were of full-thickness destruction and required grafting, but specific quantitative information in this regard is not given. These patients ranged in age from 18 to 60 years. Eleven of the 12 were thought to have been in good nutritional state prior to injury. One patient was a young woman of 29 who was a chronic alcoholic. However, she had normal fat deposits and no clinical evidence of vitamin deficiencies. Three patients, aged 44 to 75, had less severe burns involving between 15 and 20 per cent of the body surface. No statement is made regarding their nutritional states prior to injury.

Multiple measurements of metabolic rate were made in each patient, beginning early following trauma and extending throughout convalescence. An attempt was made to approximate basal conditions by making the measurements early in the morning in

the patient's private room, with the patient remaining in bed. No food was eaten during the night preceding the determination, but a few patients studied in the first days after injury had received an intravenous injection (type and quantity not specified) as part of their fluid management during the night. However, the authors make the statement that "the emotional state in some of these patients did not always correspond to the accepted standards for the determination of the basal metabolic rate."

All patients were considered to have been euthyroid prior to injury. The protein-bound iodine concentration in the serum and the uptake of I^{131} by the thyroid gland were measured in 8 of the 12 severely burned patients and in one of the 3 moderately burned patients. Seven of the 9 patients had two such determinations, and one had three determinations, during their hospital course.

The metabolic rates of the 3 patients with burns of moderate severity were normal or only slightly elevated. In contrast, an increase in metabolic rate to plus 30 to 60 per cent was observed early after injury in the majority of the severely burned patients. The oxygen consumption rate gradually declined, but continued high for as long as two months in many of the patients. No significant changes in concentration of the protein-bound iodine or in I^{131} uptake by the thyroid were observed, early or late, in either the severely or moderately burned patients.

Observations of metabolic rate were also made in 13 unburned patients. Six of these were observed before and after major surgical procedures. No specific statement is made regarding their preoperative nutritional states. The operations consisted of two herniorrhaphies, two hysterectomies, one vagotomy, and one unilateral adrenalectomy in a patient with Cushing's disease. No postoperative complications occurred. There was a slight rise in the metabolic rates (up to 10 to 15 per cent) for a few days, but on the seventh postoperative day the rates had returned to the preoperative levels.

Studies of oxygen consumption in 6 patients with perforated peptic ulcers closed surgically within the first hours after perforation are also reported. No mention is made of their nutritional states prior to the perforations. These patients were studied to determine the effect of a chemical peritonitis, the superimposed anesthesia and operative trauma. Further, the intravenous preoperative and postoperative regimens of these patients closely approximated those of some of the severely burned patients. Their metabolic rates were considerably elevated (plus 40 to plus 100) in the first few days after perforation and operation, but the oxygen consumption returned to normal by seven to ten days. No measurements of I^{131} uptake by the thyroid or of the serum protein-bound iodine were made in these patients. Thus, although the metabolic rates in the ulcer patients increased initially after perforation to about the same extent as did the metabolic rates in the patients with burns, the period of elevated oxygen consumption was considerably longer (two months as compared with ten days) in the latter. This emphasizes again the intensity of the metabolic derangement following thermal injury.

In a discussion of the basis for the increased oxygen consumption of the severely burned patients, Cope *et al.* mention as theoretic possibilities an increased activity of certain of the endocrine glands, the specific dynamic action of the high protein diet fed these patients, fever, and an increased local metabolism of the wounds. They point out that the findings of normal protein-bound iodine levels in the serum of the burned patients and of essentially normal uptakes of I^{131} seemingly rule out increased thyroid activity as the cause of the elevated metabolic rate. They also feel that the increased activity of the adrenal cortex known to follow thermal injury, as mentioned above, is coincidental rather than causal in

the elevation of the metabolic rate. Thus, patients with Cushing's disease and known hyperactivity of the adrenal glands usually have subnormal, not elevated, metabolic rates. Similarly, the metabolic rate falls in patients with arthritis receiving ACTH or cortisone. The lowering of the metabolic rate in these circumstances may result from a depression of thyroid function by excess adrenal cortical hormones.

Epinephrine is known to increase the metabolic rate, and an increased secretion of epinephrine occurs in the very early period after injury. However, Cope and his co-workers point out that it is unlikely that epinephrine is secreted at a high enough rate over a long enough time to account for the persistent elevation of the metabolic rate (up to two months) in the severely burned patient.

Many of the severely burned patients receive high protein, high caloric dietary intakes. To determine the effect of such a diet *per se* on metabolic rate, a normal male subject was placed on a diet of about 4000 calories per day. The protein part of his intake was first at a level of 30 to 40 g. of nitrogen per day, then dropped to a level of 8 g. of nitrogen per day, and then raised to the high level again. The total caloric intake was kept relatively constant throughout the study, but no statement is made of the relative proportions of dietary carbohydrate and fat during the different periods. Over the thirty-six days of study, the metabolic rate of this subject stayed within a normal range and did not appear to change significantly with the varying protein intakes. Similarly, only minor elevation of the metabolic rate was observed in the patients with moderate burns, although their dietary intakes were similar to those of the severely burned patients. Further, later in the convalescence of the severely burned patient, the metabolic rate falls despite a continuing high, or even higher, food intake. The patients with perforated peptic ulcers were on a limited food intake during the first few postoperative days, the time during which their metabolic rates were markedly elevated. The authors conclude, then, that the high level of dietary intake plays no important role in the elevation of the metabolic rate of the severely burned patients. However, no severely burned patient with a low dietary intake is reported.

Fever is known to influence the rate of oxygen consumption. For each degree (Fahrenheit) rise in temperature, there is a 7 per cent increase in the metabolic rate. Although fever probably plays a role in the elevated metabolic rate of the severely burned patient, Cope *et al.* observed that the temperature rises in the patients were irregular and did not correlate with the metabolic rate.

The authors have considered the possible effects of the local metabolism of the burned wounds. They speculate that since there is so much cellular and chemical activity in the local area, presumably the rate of oxygen consumption is increased in these areas, and that it is perhaps this activity, multiplied by the extent of the wound, which determines the metabolic rate of the burned patient. In this regard, they point out the correlation of the increased over-all metabolic rate with the extent of the wound area. However, specific information on the actual metabolic rate of the burned areas is not available.

It would appear that the prolonged and marked elevation of metabolic rate in the severely burned patient may account, in part, for the progressive malnutrition often seen in such patients. Although the pathogenesis of the elevated metabolic rate is not yet clear, it is likely that multiple factors are operative. Data as to specific tissue metabolism are needed. In the meantime, it seems reasonable to meet the increased metabolic demand by an increased dietary intake, but what the optimal levels and proportions of the various metabolites in the diet should be has not yet been elucidated.

DIETARY FACTORS IN THE ETIOLOGY OF DIABETES MELLITUS

The incidence of diabetes mellitus differs greatly in various countries of the world. It has been generally found to be highest in areas where medical care and general economic welfare are the highest. The increased frequency of the disease under such conditions has been attributed by E. P. Joslin ("The Treatment of Diabetes Mellitus," *9th ed. rev., Lea and Febiger, Philadelphia (1952)*) partly to more adequate diagnostic facilities. The importance of diet has also been suggested by H. P. Himsworth (*Clin. Sci.* **2,** *117 (1935)*), who made a correlation of the incidence of diabetes and the composition of the diet. He concluded that diabetes was most prevalent where diets rich in fat are consumed. A similar conclusion was reached by K. Suvarnakich (*Nutrition Reviews* **8,** *289 (1950)*). The low incidence of diabetes in Thailand was attributed to the national diet based on rice. Dietary analysis of the diet of 137 Thai soldiers indicates that fat accounted for but 10 per cent of the nutrients and protein but 9 per cent.

The theory that a diet rich in fat predisposes to diabetes mellitus is not supported by the observations in Iceland of V. Albertsson (*Diabetes* **2,** *184 (1953)*). This physician has made a careful study of the incidence of diabetes using a number of case-finding methods. Questionnaires were sent to all physicians in Iceland. A detection drive was carried out in a suburb of Reykjavik in which urinalyses for sugar were done on 59 per cent of the town's 2500 inhabitants. Blood sugars were done on all individuals over the age of 30 years. A careful search for diabetic patients was also made by Albertsson in his large private practice. On the basis of all available evidence it was estimated that there are about 140 known diabetic subjects in Iceland, or an incidence of less than one per 1000. The mortality statistics indicate that the annual diabetic death rate varies from 1.9 to 4.0 deaths per 100,000 living inhabitants. The diabetic death rate in the city of Reykjavik has been consistently higher than in Iceland as a whole. This figure can be compared to a rate of 26.9 for the United States and 48.2 for New York City as given by Joslin (*loc. cit.*).

In certain areas of the world the low incidence of diabetes can be attributed partly to the short life expectancy. This is not the case in Iceland. During the period 1931–1940 the life expectancy for males was 60.9 years and for females it was 65.6 years. The inadequacy of medical care in many parts of the world may contribute to an apparent low incidence of diabetes due to failure of diagnosis. Although Iceland is sparsely settled, improved communications have made medical practitioners quite generally available. The ratio of one physician for each 800 to 900 inhabitants equals that of much of the United States. The high life expectancy argues in favor of good general medical care.

The diet in Iceland has for many years been rich in protein and fat ingested as milk, meat and fish. The carbohydrate content of the diet one hundred years ago was estimated to be only 32 per cent. The wider use of white bread, potatoes and white sugar in recent years has caused a rise in carbohydrate intake which in 1940 in towns had reached 44.2 per cent. During the same period the foods of animal origin which had comprised 80 to 85 per cent of the diet now account for only 45 to 58 per cent of the diet.

The rarity of obesity observed in both Thailand and Iceland may be more significant than the actual composition of the diet. Albertsson noted that forty years ago overweight individuals were rare. Recent economic gains accompanied by shorter hours and less physical exertion has resulted in an increased incidence of obesity. This tendency may be responsible for the increase

in diabetes observed in the urban areas in recent years.

These studies of the role of diet in predisposing to diabetes would seem to indicate that the proportion of carbohydrate, fat and protein may not be important. An excessive caloric intake associated with a diminished physical activity may be the more important factor in producing diabetes. The importance of avoiding excess body weight in the prevention of diabetes is emphasized by these studies.

PROLONGED POTASSIUM DEFICIENCY IN MAN

The metabolic effects of restricted potassium intake in man have been reported by D. A. K. Black and M. D. Milne (*Lancet* **I,** *244* (*1952*); *Clin. Sci.* **11,** *397* (*1952*); *Nutrition Reviews* **10,** *163* (*1952*)). A diet containing less than 10 mEq of potassium per day was fed to 2 normal men for six and seven days with suitable control periods. The potassium deficits during potassium depletion totalled 208 and 289 mEq. On the low potassium diet, serum potassium fell and there was a parallel rise in serum bicarbonate. A retention of sodium occurred during potassium depletion and there was an increase in extracellular fluid volume at the expense of intracellular fluid volume.

Our knowledge of potassium deficiency in man has been extended by a paper of W. H. Blahd and S. H. Bassett (*Metabolism* **2,** *218* (*1953*)). These authors have reported a prolonged metabolic study of a healthy 35 year old man. For two periods of five days each he was allowed to eat a diet containing 91 mEq of potassium and 138 mEq of sodium. He was then shifted to a diet containing 14 mEq of potassium and 92 mEq of sodium for thirteen five-day periods. During the last two five-day periods the low potassium diet was supplemented with potassium citrate containing 86 mEq of potassium daily. The study was terminated by two five-day periods of a diet containing a normal potassium content. Complete sodium, potassium, chloride and nitrogen balances were determined.

Following the institution of the low potassium diet, the potassium balance became negative. At first considerable potassium was lost from the body in the urine. Over the period of fifteen days the urinary potassium gradually fell to a level which continued unchanged throughout the rest of the low potassium period. Despite maximal renal conservation of potassium, a negative potassium balance of from 1 to 13 mEq a day continued during periods four through eleven. The cumulative potassium loss for the fifty-five-day period was 278 mEq. This is a minimum figure because additional potassium was lost from the skin and mucous membranes. The serum potassium level fell from 4 to 3 mEq per liter. During the period when potassium was being lost from the body there was a retention of sodium and chloride totalling 1102 and 649 mEq respectively. When potassium was restored to the diet a retention of 273 mEq of this ion occurred.

Exchangeable potassium was determined with K^{42} during the latter part of the potassium depletion period and following potassium repletion. Values of 3228 mEq and 3450 mEq were obtained for these two periods. Although the difference between these figures approximates the potassium retained during repletion it was not considered significant by the authors.

As in the studies of Black and Milne (*loc. cit.*), no clinical alterations were observed. Weight was maintained and there was no evidence in the nitrogen balances of protein breakdown. Blood pressure, electrocardiogram and ergograms remained unchanged.

The observations of Blahd and Bassett

differ from those of Black and Milne in that the potassium restriction was less stringent and was continued for a longer period of time. Good agreement in the degree of potassium loss and sodium retention was obtained. The data presented in these articles are a valuable addition to our knowledge of electrolyte metabolism.

ANOREXIA

It was in 1888 that Sir William Gull described the strange malady labeled "anorexia nervosa," the victims of which frequently starve themselves to death in the absence of known organic defects (W. Gull, *Lancet* **I,** *516 (1888)*). The ideas concerning the etiology of this disease have varied from a mechano-surgical point of view, emphasizing a downward displacement of the stomach (gastroptosis) as the critical factor, to complex psychiatric and psychoanalytic interpretations.

A series of 45 cases of nervous anorexia was described and analyzed by H. Hertz (*Acta Med. Scandinav., Suppl.* **266,** *523 (1952)*). The first striking fact, noted also by the earlier observers, was the discrepancy in the sex distribution, only 2 of the patients being male. This seems to indicate that hormonal factors somehow are involved, but the relationship may be quite indirect and the endocrinologic details are not clear. The patients lacked symptoms characteristic of Simmond's disease (pituitary cachexia), a condition of premature aging due to atrophy of the hypophysis, and the x-rays revealed no anatomic abnormalities in the region of the skull in which the gland is located.

The output of gonadotropic estrogenic hormones tended to be low in all cases. In more than one half of the female patients menstruation was infrequent or absent. Menstrual disorders of this type are common in women exposed to prolonged caloric deficiency. With reference to the age of the patients, the disease was most frequent in adolescent girls and young women (age group 14 to 25). J. J. Déjerine and E. Gauckler ("Functional Manifestations of Psychoneuroses," (in French) *Paris (1911)*) believed that this is the age at which a *primary* anorexia develops. The term *secondary* anorexia, as used by these authors, refers to a failure of the desire for food resulting from known mental diseases.

The treatment of the psychologic aspects of the disease in Hertz's paper is very cursory. Known psychologic trauma (such as conflict with parents, a divorce, death of a fiancé, or a broken engagement) was associated with the development of nervous anorexia in less than one half of the cases. In about one fourth of the patients anorexia was preceded by disturbances of the gastrointestinal system, such as constipation and diarrhea. The author accepts the suggestion put forth by K. Faber (*Intern Med. (Copenhagen), p. 165 (1930)*) that in these cases anorexia develops from the fear of eating foods which may cause the digestive disturbances. Prognosis appears to be best in the younger individuals, *i.e.*, in that group of patients in which the psychologic traumas are most frequent. Older patients, in whom the onset of anorexia is not associated with an obvious psychologic trauma, are likely to continue in a chronic asthenic condition.

The study of anorexia nervosa is of theoretic interest and the improvement of technics for its treatment is of clinical importance. Practically, however, a much more acute problem is the loss of "appetite" which is such a frequent and early accompaniment of a variety of organic diseases. Simple anorexia, easily brought on by pain and coming on with the malaise of most acute infections, is one of the most common symptoms in medicine and perhaps the single most important cause of undernutri-

tion in sick people. Yet our understanding of the physiologic basis of this phenomenon is inadequate. In some types of somatic illness a peripheral origin of the disturbed desire for food is known or at least suspected. Thus, in patients with duodenal ulcer or diabetes the hypertonicity (the increased muscular tonus) of the stomach wall is considered responsible for increased hunger while hypotonicity is thought to account for the lack of desire for food in pulmonary tuberculosis and in thiamine deficiency. It is known that appetite, which may be differentiated from the experience of hunger (resulting normally from vigorous gastric contractions) and which is largely a cortical phenomenon, plays an important role in the complex desire for food. Serving "appetizing" food is a valuable contribution of the hospital dietitian to the maintenance of a reasonably normal nutritional status of the patients on medical and surgical, as well as on psychiatric wards.

In this context, R. W. Keeton's analysis of the physiologic mechanism involved in the normal intake of food and its modification by disease, and the efforts to combat anorexia by an appetite-training regimen are of interest (*J. Am. Dietet. Assn.* **26,** *336 (1950)*).

Older individuals tend to eat less than younger persons. Thus, groups of women, aged 40 to 75 years, consumed from 300 to 500 calories less than representative samples of young women (M. A. Ohlson, P. H. Roberts, S. A. Joseph, and P. M. Nelson, *J. Am. Dietet. Assn.* **24,** *286 (1948)*). Of interest is the observation that women who did not enjoy full health consistently ate less than the healthy individuals. Unfortunately, it could not be established satisfactorily whether ill-health precipitated a partial failure of appetite or whether the ill-health was, in part, the result of a long-time practice of lowered food intake.

The problem of senile anorexia was examined by N. Vinther-Paulsen (*Geriatrics* **7,** *274 (1952)*). He emphasized that among the aged the tendency to lose the desire for food is widespread and that undernutrition and malnutrition may importantly contribute to senile debility. It has been observed under experimental conditions (*Nutrition Reviews* **7,** *78 (1949)*) that prolonged reduction of caloric intake in initially normal, healthy young men results in a syndrome many aspects of which resemble old-age debility (weakness, feeling of cold, slow movements, apathy). A condition resembling senile debility was observed by T. D. Spies and H. S. Collins (*J. Gerontology* **1,** *33 (1946)*) in middle-aged patients suffering from malnutrition.

Vinther-Paulsen reports that symptoms of nutritive failure are very common among old weak persons living by themselves. During a six-month period of observation of all the patients admitted to the Hospital for the Aged in Copenhagen, 109 persons exhibited marked reddening of the tongue and abnormality of the papillae (glossitis), considered by the author as specific criteria of malnutrition in old persons, while the tongue was normal in 124 individuals. While the specificity of this symptom is questionable, the author's data on a group of 32 women, ranging in age from 67 to 96, are of interest. The method used is not described, but it is stated that amount and composition of the daily food intake was recorded for two one-week periods. Caloric content and the amounts of a variety of nutrients were calculated from standard food tables. The patients exhibiting glossitis had a definitely lower total food intake (below 1250 calories) and the intake of most specific nutrients was reduced proportionately. Thus we are apparently dealing with a quantitative rather than a qualitative dietary insufficiency. The intake of vitamins C and D showed little difference in the two groups. The intake of milk was very low, due in part to the common belief that milk furthers constipation.

Our knowledge of the food requirements of very old people is inadequate and Vinther-

Paulsen's attempt to set up such values may be of some interest (*Rev. méd. de Liège* **5,** *652 (1950)*). In the present study (*Geriatrics, loc. cit.*) only the intakes of energy (about 1600 calories), calcium (0.6 g.) and vitamin A (2400 I.U.) of his "control group"—patients with normal tongues—were close to or identical with the assumed requirements. In all other instances these requirements were higher; in the case of several nutrients (protein, iron, thiamine, niacin, vitamin D) they were substantially higher.

The etiology of anorexia frequently found in old age is not fully understood, but it is certain to be complex, including medical, psychologic, and sociologic factors. The clinical impression is that temporary anorexia is one of the most common accompaniments of physical disease; older people regain appetite less readily than younger individuals. There are such factors as the lowered content of hydrochloric acid in gastric secretions and a decreased secretion of digestive enzymes. Poor teeth interfere with the use of foods requiring chewing. Loneliness, economic deterioration and physical difficulties in getting around may play important roles in lowering the food intake and, at times, in leading to bizarre and unwholesome food habits.

The tendency to anorexia in old age is a phenomenon deserving further study. While it is not yet clear what percentage of old patients exhibiting general weakness in the absence of demonstrable disease is due to prolonged malnutrition, certainly the importance of an adequate diet as a prophylactic measure against senile debility deserves emphasis.

EFFECTS OF PRODUCTION PROCEDURES ON THE FOOD VALUE OF CARROTS

Carrots are very generally used the year around as a vegetable on the American dinner table. Their food value has been extensively studied, but with little or no consideration as to possible effect of field practices and marketing procedures on food value of the resultant product. A survey of these effects on carrots in California was recently completed by M. Yamaguchi, B. Robinson, and J. H. MacGillivray (*Proc. Am. Soc. Hort. Sci.* **60,** *351 (1952)*).

Carrot roots were taken from numerous areas in California from fields being harvested for eastern shipment. Except for the variety studies, the variety Imperator was used. Roots were stored in crushed ice during transit to the laboratory. A three-pound sample was used for analysis, consisting of one segment from the edible portion of each of 50 to 125 roots. After being finely chopped and mixed, aliquots were used for numerous chemical analyses. Carrots were first shown not to change during a three-day period in crushed ice, in the following constituents: energy, protein, calcium, iron, phosphorus, carotene (alpha- and beta-carotenes separately), ascorbic acid, thiamine, riboflavin and niacin. This time interval permitted transportation for 600 miles from Imperial Valley to the laboratories of the University of California at Davis.

No important differences in contents were found when whole roots of different commercial sizes were compared, from two locations and on several dates. When carrots were divided into peeling (13 per cent of carrot), phloem (72 per cent), and xylem or core (15 per cent), some very significant differences appeared. These are of particular significance to plant breeders who may be interested in changing certain sections of the carrot root. The phloem, constituting most of the carrot, is high in energy and vitamin A. The peeling, often discarded in culinary practices, is higher in calcium, iron and thiamine than the other sections. The

core is high in phosphorus. Protein, ascorbic acid and riboflavin were uniform in these sections.

The effect of age at harvesting time was studied on two lots grown at Davis, one reaching marketable age in late November and one in late June. Six samplings were made on each lot. As carrots approach the best time for harvest, the tops decrease in relative amounts. The root contents of energy, calcium and vitamin A increase in a gradual manner. Other constituents do not change much. The spring crop was lower in protein and phosphorus but higher in vitamin A than the fall crop at corresponding ages.

The time of year and geographic area were both shown to be important when carrots currently being harvested for market were sampled from three distinct regions: Imperial Valley, Monterey County, and Yolo County (Davis). Monterey carrots were low in protein and high in calcium. Imperial roots were low in phosphorus, and Yolo carrots were high in iron. Soil differences may have been important here. Both Yolo and Imperial roots were much higher in ascorbic acid content than Monterey roots, perhaps due to longer days of bright sunshine in these interior areas. Winter-harvested carrots were higher in energy, protein and iron, but lower in vitamin A and calcium than those harvested in spring. The ratio of alpha- to beta-carotenes was lower in the carrots grown during the cooler seasons than in those grown in the warmer seasons by a factor of about two. This was true in the variety tests and in Imperator carrots grown in different geographic areas of California.

Four common varieties, Imperator, Red Core Danvers, Red Core Chantenay and Nantes, were grown near San Jose for variety comparison. Imperator was highest in energy, calcium and phosphorus and relatively high in most nutrients. Nantes was low in phosphorus, vitamin A and riboflavin.

ADAPTATION TO LOW CALCIUM DIETS

The inconsistencies between the recommended allowances for calcium and the dietary practices in many parts of the world are well known. In the United States the level of calcium intake is repeatedly cited as being low while at the same time the clinical evidence for symptoms directly attributable to calcium deficiency are very rare in the adult population. The relation of calcium intakes to the occurrence of postmenopausal osteoporosis requires further study. The weaknesses of the data upon which the recommended allowances for calcium are based have been discussed (*Nutrition Reviews* **10,** *257 (1952)*).

Decalcification in elderly adults and animals as indicated by negative calcium balances and x-ray data is commonly observed. Regardless of the cause, the frequent fractures which occur in elderly females especially is a serious disability and obviously worthy of study. High calcium diets do not appear to be particularly beneficial therapeutically, and F. Albright (*see Nutrition Reviews* **5,** *249 (1947)*) attributes the conditions to faulty matrix metabolism rather than lack of calcification per se. Therapeutic trials with the sex hormones as well as the sex distribution of the disease points to a major role of such hormones. Nevertheless, a recent article records an apparent relationship between the dietary habits of women over the age of 65 and the occurrence of broken femurs. In old rats and hamsters G. G. Kane and C. M. McCay (*J. Gerontol.* **2,** *244 (1947)*) found that in short-term studies high levels of calcium intake can prevent the negative calcium balances. Suggestive evidence of high requirements in elderly women is available (P. H. Roberts, C. B.

Kerr, and M. A. Ohlson, *J. Am. Dietet. Assn.* **24,** *292 (1948)*).

Logical reasoning may lead one to the following premise: if the ability of the old animal to retain calcium is impaired, it might be valuable for an animal to reach old age with maximum or near maximum stores of calcium. Thus he would at least have more to go on when the calcium-retaining mechanisms, whatever they may be, begin to fail. High calcium diets prior to old age might thus be beneficial. This hypothesis has been tested in rats in a recent contribution by K. M. Henry and S. K. Kon (*Brit. J. Nutrition* **7,** *147 (1953)*) with interesting results.

The main part of the studies reported consisted of large groups of rats fed three different diets containing 0.13, 0.4 and 0.8 per cent calcium. The basal low calcium diet consisted of one part skim milk and nine parts whole wheat with 4 per cent of a low calcium-salt mixture replacing 4 per cent of wheat. Additional calcium in the other diets was supplied by additions of calcium phosphate. Male weanling rats were started upon these diets. At intervals during a two-year period groups of animals from each dietary regimen were placed in metabolism cages and the calcium balance was studied over a three-week period during which time all of the animals received the low calcium diet containing 0.13 per cent calcium. Each such study was preceded by a one-week adjustment period on the same diet when the excreta were not collected. Other groups of animals fed similar diets and treated in the same manner were killed at intervals during the study for the determination of ash, calcium and phosphorus in the bones.

As might be expected, the bone analyses showed that the rate of calcification was dependent upon the calcium content of the diet. The differences were not marked in the three groups, but at 3 months of age, for example, the calcium content was 21.7, 22.8 and 23.5 per cent for the three groups, respectively. At 1 year of age, however, the bone ash and calcium and phosphorus content reached the same level in all three groups and did not change during the next year. The metabolic studies showed a continual decrease in calcium retention in all animals as the animals became older. This effect was more marked in the animals which received the higher calcium diets and after 15 months of age they were always in negative balance when fed the low calcium diet. In only one test period were the animals which had received the lowest calcium diet found to be in slight negative calcium balance.

After age 21 months animals from all three groups were given the low calcium diet and their balances were tested after three months on this regimen. Although the animals from the two higher levels of calcium intake were losing less calcium than at 21 months they were still in negative balance, while animals which had received the low calcium diet throughout their life were in slight positive balance.

A second series of somewhat similar studies is reported in which animals were fed a diet, either with or without vitamin D, and which contained 0.7 to 0.8 per cent calcium and phosphorus, for approximately a year. Calcium balance studies on this diet, or on one containing 0.25 per cent calcium and 0.4 per cent phosphorus, failed to show any effect of vitamin D on the calcium metabolism. These results fail to support the view of R. Nicolaysen (*Acta physiol. Scandinav.* **5,** *200 (1943)*) that the calcium metabolism in the rat is controlled by an endogenous factor effective only in the presence of vitamin D.

The authors conclude from these studies that the calcium retention, before calcification is complete, is influenced by the body stores of calcium. After calcification is complete the ability to retain calcium is not related to the calcium content of the bones since all of the animals reached the same calcium content. Thus it appears that the way in which the calcium is accumulated

determines the plane of calcium metabolism. Stores acquired slowly appear to be held more tenaciously, or possibly have a slower rate of turnover. Regardless of the mechanism involved, it is of importance that the adaptation to low calcium diets throughout life extended to the senescent animal and was accomplished without any detectable change in the calcium stores. Insofar as data are available, the adaptation of rats and human beings to low calcium diets would appear to be similar. The feeding of a low calcium diet to the senescent rats in this study resulted in some degree of adaptation, apparently at the expense of body stores after a three-month period, although complete adaptation had not yet been achieved by the rat previously adapted to the high calcium diet. On a time basis, three months in the life span of the rat would compare to about eight years in man. The evidence on man also indicates that adaptation is a very slow and prolonged process.

One may infer from these studies that the commonly observed negative balances in elderly people may usually be due to the consumption of lower calcium diets than those to which they were previously accustomed. The usefulness of attempts to build up calcium stores as a means of improving the status during old age is not supported by this work. The possibility that adaptation to high calcium diets may be disadvantageous in later life may deserve some serious consideration.

ANTITHYROTOXIC PROPERTIES OF DIETARY FAT AND LIVER RESIDUE IN RATS

The increased dietary requirements which are produced by feeding experimental animals thyroid substances have been discussed previously (*Nutrition Reviews* **6,** *54* (*1948*); **7,** *183* (*1949*); **8,** *141* (*1950*)). Evidence has been obtained that, in addition to an increased requirement for calories, there is an increased requirement for vitamin A, thiamine, pyridoxine, pantothenic acid, niacin, vitamin B_{12}, and vitamin E. In addition to deficiencies of these recognized vitamins, deficiencies of hitherto unrecognized dietary factors have been suggested by the work of B. H. Ershoff (*Proc. Soc. Exp. Biol. Med.* **64,** *500* (*1947*)) and that of J. J. Betheil, V. D. Wiebelhaus, and H. A. Lardy (*J. Nutrition* **34,** *431* (*1947*)), who demonstrated the beneficial effects of dried liver residues and yeast on the growth of thyrotoxic rats fed purified diets supplemented with various combinations of synthetic vitamins. It was shown by the latter group of investigators that the liver fraction was stable for a wide range of temperature and hydrogen ion concentration.

The antithyrotoxic effects of dietary fat have been studied by B. H. Ershoff (*J. Nutrition* **39,** *259* (*1949*)). Previously a protective effect of fats, and perhaps more particularly unsaturated fatty acid, had been observed by others in experimental hyperthyroidism. In reviewing the previous work Ershoff concludes that at least part of the benefit could be attributed to increased caloric intake or the ingestion or absorption of fat-soluble vitamins, but fatty acids, particularly unsaturated fatty acids, could also modify directly the inhibition of growth produced by excess thyroid hormone. In his experiments with thyrotoxic rats Ershoff found that full-fat soybean meal had a protective effect on growth without causing alteration of the basal metabolic rate. Fat-free soybean meal did not support similar growth. Restoration of more normal growth of thyroid-treated rats on a fat-free soybean meal diet was achieved with soybean oil, liver residue, or vitamin B_{12}. It would seem, therefore, that growth retardation of thyrotoxic rats on a low fat regimen was more complicated than a simple conditioned deficiency of essential fatty acids.

This problem has been studied further by B. H. Ershoff (*Metabolism* **2,** *175* (*1953*)),

who has compared the effects of B-vitamins, fat supplements, and liver residue on the growth and survival of hyperthyroid rats. In his studies purified diets containing 0, 2 and 10 per cent of fat were used. Vitamin supplements were adequate for the normal growth of euthyroid rats. Each diet was augmented as indicated below and fed to five groups of rats: (1) basal ration alone, (2) basal diet plus thyroid powder, (3) basal diet plus thyroid powder and generous amounts of all the B-vitamins including biotin, folacin, para-aminobenzoic acid, inositol and vitamin B_{12}, which were absent in the basal diet, (4) basal diet plus thyroid powder and 10 per cent water-insoluble liver residue, (5) basal diet plus thyroid and water-insoluble liver residue which had been thoroughly extracted with organic solvents. The experimental diets were fed for six weeks.

The addition of thyroid powder to the basal diet containing no fat was followed by a growth retardation and increased mortality. Increased growth and survival occurred in rats fed increasing amounts of dietary fat without other supplements. On a fat-free diet the addition of B-vitamin supplements was without effect. On the 10 per cent fat diet, B-vitamins completely overcame the retardation of growth produced by thyroid feedings. On the 2 per cent fat diet the B-vitamins were only partially effective. Liver residue was protective at all three levels of dietary fat intake. The fat-free liver residue proved to be as active as the crude material.

The nature of the protective factor in liver residue remains to be discovered. The author cites unpublished data which indicated that the addition of 80,000 and 200,000 units of pyruvate oxidation factor (lipoic acid) per kilogram of diet did not promote the growth of hyperthyroid rats. The authors suggest that the synergistic effect of dietary fat and B-vitamins might be due to the favorable influence of these nutrients on the synthesis or utilization of a factor similar to that found in liver residue.

It would seem that the dietary deficiencies of the hyperthyroid rat may be multiple and overlapping. With the proper selection of an experimental diet containing no fat, the evidence presented indicates that the beneficial effect of liver residue cannot be reproduced by any known nutrient. With the aid of this assay system, isolation and identification of the active principle should be possible.

COLOSTRUM AND ZINC DEFICIENCY IN THE MOUSE

There is a growing body of evidence, some circumstantial, some controversial, indicating beneficial effects resulting from breast feeding. One of the important questions related to this problem is the function of colostrum in the nutrition of the newborn animal. An interesting experimental approach has been used by H. Nishimura (*J. Nutrition* **49**, *79* (*1953*)). Newborn mice of an unknown strain were foster-nursed by females already in the thirteenth to eighteenth day of lactation. The young raised in this fashion showed a variety of deficiency symptoms which were curable by the administration of zinc. It is implied that colostrum contains unusually large quantities of this metal, and that its availability to the newborn provides the zinc stores necessary for normal early growth. Adequate evidence is provided to show that the deficiency symptoms are not caused by any lack of ability on the part of the female to provide adequate quantities of milk.

The growth rates of the foster-nursed offspring were somewhat less than those of the control mice. Unfortunately, no statistical treatment is offered to test the significance of this difference. Daily examination of the developing foster-nursed offspring showed some acceleration in the eruption of the lower incisors and also in the separation of the eyelids. Whether this difference is

statistically significant is difficult to decide on the basis of the data furnished. The author states that ossification of caudal vertebrae was somewhat retarded. The most striking external change observed in these experiments was the retardation of hair development, which led to considerable thinning and often to alopecia. In addition, the skin became glossy and somewhat thickened. This was followed by extensive scaliness.

Histologic studies showed that the epidermis was three to four times its normal thickness, with extensive desquamation and hyperkeratinization. Mitosis was considerably increased in the germinal layer of the skin of the foster-nursed offspring. Very little subcutaneous fat was found in the experimental animals. This is what one would expect to find in any deficiency state. Structural changes were also observed in hair and hair follicles.

Several experiments are described which demonstrate satisfactorily that mother's milk during the first few days after parturition contains some factor which is not provided in adequate amounts by milk secreted later during the lactation period. Although the administration of thiamine gave some relief, the only effective protection was given by zinc salts, a single dose on the day of birth being sufficient for protection.

The necessarily brief description of hair growth in zinc-deficient mice raises some important questions. Is there, as the author implies, a reduction in the total number of hair follicles? If so, the case is most unusual since the number of such follicles ordinarily remains constant. Are the hairs of the deficient mice in fact poorly developed, or did the larger, regularly shaped hairs fall out, leaving behind the smaller, normally occurring zig-zag hairs? These and other questions might be answered after further study employing more rigidly controlled conditions as described by H. B. Chase, H. Rauch, and V. W. Smith (*Physiol. Zool.* **24,** *1 (1951)*).

It is somewhat disturbing to discover in this investigation indications that the nutritional status of the mouse colony employed for the investigation was not of the highest. Evidence for this can be found in the inferior rate of growth exhibited even by control animals and in the strikingly low red blood cell count of both control and experimental mice. Since there is ample evidence that the nutritional status of an animal colony may drastically influence the response to a given nutritional treatment, one is led to wonder whether offspring of a more adequately nourished mouse colony might not show a somewhat different response to foster nursing.

LIVER KYNURENINASE ACTIVITY AND TRYPTOPHAN METABOLISM IN VITAMIN B_6 DEFICIENCY

The biologic synthesis of niacin from tryptophan includes formation of kynurenine and anthranilic acid as intermediate products of metabolism (*Nutrition Reviews* **9,** *272 (1951)*; **10,** *272 (1952)*). It has been demonstrated that pyridoxal phosphate functions as a coenzyme at the stage of splitting of kynurenine or hydroxykynurenine to release alanine and form anthranilic or hydroxyanthranilic acids (C. E. Dalgliesh, W. E. Knox, and A. Neuberger, *Nature* **168,** *20 (1951)*). The activity of the responsible enzyme, kynureninase, is decreased in liver, and the substrates, kynurenine and hydroxykynurenine, accumulate in tissues of vitamin B_6-deficient animals (M. Mason and C. P. Berg, *J. Biol. Chem.* **195,** *515 (1952)*; Dalgliesh, *Biochem. J.* **52,** *3 (1952)*).

These observations have laid the background for investigations of rates of enzymatic reactions responsible for the formation and degradation of kynurenine in

vitamin B_6-deficient animals. In such animals kynurenine and its derivatives are lost in the urine. However, the increased accumulation of the substrate in tissues and its excretion might conceivably result from a variety of changes in rates of synthesis or splitting. Kynurenine is formed by the action of tryptophan peroxidase. The activity of this enzyme has been studied in the liver of vitamin B_6-deficient rats and was found to be unimpaired. In addition, the rate of reaction was increased when tryptophan was administered to the deficient animals (W. E. Knox, *Brit. J. Exp. Path.* **32,** *462 (1951)*).

The potential rates of kynurenine removal have been determined by the same investigator (W. E. Knox, *Biochem. J.* **53,** *379 (1953)*). To facilitate these studies a new method of determining kynureninase activity was developed and was demonstrated to measure the total potential activity of the enzyme. Data concerning reaction products, substrate concentration, pH optimum, specificity, and the coenzyme are recorded. Of the tissues studied kynureninase activity was greatest in liver. Kidney tissue was only 10 per cent as active. The liver was considered, therefore, to be the organ of primary significance in determining the quantity of kynurenine split in the intact animal.

The average kynureninase activity in the livers of a group of normal rats was shown to be 11.1 micromoles per gram dry weight per hour. Addition of pyridoxal phosphate to the medium increased this mean value to 14.3. Activities were decreased in the livers of vitamin B_6-deficient rats, averaging 5.9 micromoles per gram dry weight per hour, but increasing almost to normal, 12.7, with introduction of the coenzyme, pyridoxal phosphate, into the medium. The latter finding gave evidence that the enzyme protein was maintained during deficiency and needed only coenzyme to resume activity. The weight of the livers of the deficient rats was less that that of normal control animals, so that the effective decrease in kynureninase activity was greater than the 50 per cent decrease indicated on the basis of reference of activity to unit weight.

The intraperitoneal administration of 2 millimoles of either kynurenine or tryptophan six hours before normal rats were killed failed to effect an increase in kynureninase activity. This was evidence of lack of adaptation of enzyme activity to increased quantities of substrate. In contrast, the kynurenine-forming enzyme, tryptophan peroxidase, tripled in activity after administration of tryptophan.

The publication of these data permits more explicit definition of the defect in tryptophan metabolism which accompanies vitamin B_6 deficiency. The liver is demonstrated to be the chief site of formation of kynurenine from tryptophan as well as the major organ of conversion of kynurenine to anthranilic acid and alanine. In the livers of normal animals rates of the two reactions are very similar, being 9.3 and 11.1 micromoles per gram dry weight of liver per hour, respectively. Kynureninase activity is reduced by half in vitamin B_6-deficient animals, whereas tryptophan peroxidase retains normal rates of activity. In deficiency, therefore, the stage is set for accumulation of kynurenine and conversion into metabolites with the intact side chain. These are then excreted in urine. Furthermore, administration of tryptophan permits greater activity of tryptophan peroxidase and results in even larger accumulations of kynurenine. Therefore, the primary metabolic block seems to be well established on the basis of decreased kynureninase activity in vitamin B_6 deficiency. Although this enzyme had been known to require pyridoxal phosphate as a coenzyme and would reasonably be assumed to represent the site of metabolic block, it is indeed encouraging to see the mechanism so adequately described. It is of importance, also, to recognize the enhancement of the defect which results from increased rates of synthesis of kynurenine when tryptophan is fed.

IN VITRO STUDIES OF INTESTINAL CARBOHYDRATE ABSORPTION

The absorption of carbohydrates from the gastrointestinal lumen has been studied extensively in the whole animal. The technic devised by C. F. Cori involved the administration of a given amount of sugar by stomach tube to a rat. After a period of time the rat is killed and the sugar remaining in the entire gastrointestinal tract is measured. In larger animals methods utilizing the intubation of portions of the intestine or of isolated segments of intestines have supplemented our knowledge. From many such studies it has become apparent that there is an active transport mechanism for the nutritionally significant hexoses.

The rate of transport of each sugar differs, the sequence in the rat according to Cori being: galactose → glucose → fructose → mannose. The actual mechanism of sugar transport has been postulated by F. Verzár and E. J. McDougall ("Absorption from the Intestine," *Longmans, Green and Co., London (1936)*) to involve phosphorylation, but actual proof of such a theory has not been possible with the experimental systems thus far available.

An advance in this field has been made by W. A. Darlington and J. H. Quastel (*Arch. Biochem.* **43,** *194 (1953)*). These workers have developed an *in vitro* perfusion apparatus for segments of guinea pig intestine. The system is so designed that there is a separate perfusion system for the intestinal lumen and the external bathing medium. Provision is made for sampling the perfusing fluids without interrupting the operation of the system. The fluid used is a modified Ringer-bicarbonate solution which can be adequately aerated. Histologic study after ninety minutes of perfusion showed some degenerative changes, but no gross stripping of the mucosa.

The rates of absorption of the simple sugars have been measured with the above apparatus. When the intraluminal medium contained 0.25 per cent glucose, a 10 cm. section of intestine was capable of removing 7.1 mg. per hour. In comparison, the absorption of 0.25 per cent sorbose was at a rate of 0.5 mg. per hour. On the basis of the work of others the authors assumed that the absorption of sorbose was by a process of simple diffusion. The relative rates of absorption of the sugars was found to be galactose, 100; glucose, 100; fructose, 50; sorbose, 37. The order obtained with the perfused intestinal strips agrees quite well with that reported earlier.

The absorption of fructose was studied to determine the extent of the transformation of fructose to glucose. The extraintestinal fluid was measured for glucose and fructose when fructose was added to the intraluminal fluid. Fructose appeared in the outer solution at about the same rate that sorbose was absorbed. The total reducing activity in the outer fluid was much greater than could be accounted for by the fructose present. The nonfructose reducing material was shown to be glucose, by employing the glucose oxidase enzyme (notatin) and manometric measurement of the oxygen uptake. The authors interpret their results with fructose as indicating that the active absorption of fructose by the intestinal mucosa results in its transformation into glucose and that the free fructose which is absorbed arrives in the outer fluid by passive diffusion.

Phosphate levels of the intraintestinal and extraintestinal mediums did not change during the absorption of glucose and galactose. The presence of phosphate in the perfusion fluids was in fact not necessary for the absorption of sugars. It was possible, however, to relate the absorption of sugars to respiratory activity. When oxygen was replaced by nitrogen in the aeration gas mixture the selective reabsorption of glucose was completely abolished. Under these conditions the permeability to glucose was unaltered. Chemical blocking agents were studied and it was found that cyanide, azide, fluoroacetate, malonate and chloretone were all active in moderately high concentrations

in inhibiting glucose absorption. The most effective blocking agent observed was 2,4-dinitrophenol which was active in a concentration of 0.0001 molar. This finding was interpreted as strong evidence supporting the hypothesis that phosphorylation takes place in the absorption of glucose.

The absorption of phosphorylated intermediates of the glycolytic chain was measured. Hexose diphosphate was absorbed at a rate significantly slower than was glucose. The absorption of glucose-1-phosphate occurred at a rate which was essentially the same as that of glucose. No great importance can be attached to these observations because these esters might have been dephosphorylated prior to absorption.

It may be safely concluded that Darlington and Quastel have developed a method of great potential usefulness for the study of intestinal absorption under *in vitro* conditions. The functional adequacy of this preparation is suggested by the statement that the rate of absorption remained constant during the experimental period. It is unfortunate that this finding is not documented in the article with actual figures because of the importance of this observation in assessing the normalcy of the intestinal preparation. The results obtained with this new method are in good general agreement with those obtained with earlier *in vivo* methods. In addition, the *in vitro* studies have established the dependence of carbohydrate reabsorption on oxidative metabolism, and thus support the view that phosphorylation takes place in the course of glucose absorption.

METABOLISM OF THE PLASMA EXPANDERS DEXTRAN AND POLYVINYL PYRROLIDONE

A diminution of the circulating blood volume is one of the most important factors in the pathogenesis of wound shock. Early restoration and maintenance of blood volume at an adequate level is essential for successful treatment. Whole blood is the most effective single agent currently available for replacement therapy. However, the probable critical shortage of whole blood during a national emergency has caused a search for a suitable "blood substitute." Acacia was proposed and investigated during World War I; gelatin, dextran, polyvinyl pyrrolidone, and others during and subsequent to World War II. It soon became apparent that the term "blood substitute" was a poor one. No simple colloid solution could substitute physiologically for whole blood with its erythrocytes and other specialized components. Similarly, the term "plasma substitute" has also been discarded and in its place the terms "plasma volume extender" or "plasma volume expander" are used.

Among the commonly accepted criteria for a satisfactory plasma volume extender are maintenance of a satisfactory colloid pressure, constant and known composition, suitable viscosity, thermal and storage stability, ease of sterilization, freedom from pyrogens, absence of immediate or delayed adverse effects, absence of antigenicity, and reasonable price. Among the various agents investigated gelatin, dextran and polyvinyl pyrrolidone have proved useful in the treatment of traumatic shock.

Dextran is a polysaccharide of high molecular weight, composed of molecules connected in 1–6 and 1–4 glucosidic linkages and obtained from the capsule of the bacterium *Leuconostoc mesenteroides*. It has also been produced synthetically by an enzyme isolated from the bacteria. As produced by the bacteria, dextran is of exceedingly high molecular weight and leads to many unfavorable side reactions when infused. These disappear when the dextran particle size is reduced by partial hydrolysis. For clinical use, dextran with molecular weights of 20,000 to 200,000 is employed and appears

to fulfill most of the requirements for a useful plasma expander except for possible antigenicity on rare occasions.

The ultimate fate of dextran in the body is not known with any certainty, except for that part of the infused dextran which is excreted in the urine. In a recent study, one liter of 6 per cent dextran solution in isotonic saline was administered intravenously in fifty minutes to human subjects with a normal blood volume and subjects with oligemia induced by rapid removal of one liter of blood (J. F. Hammarsten, B. I. Heller, and R. V. Ebert, *J. Clin. Invest.* **32,** *340 (1953)*). Plasma dextran concentration and urinary excretion of dextran were similar in both groups. The cumulative urinary excretion was about 25 per cent of the infused dextran in the first hour, about 40 per cent in six hours, and about 60 per cent in twenty-four hours. During this time there was a gradual fall in the plasma dextran, concentration and total, in both groups. At the same time, a significant amount of protein was added to the plasma of the bled subjects. This amounted to 3, 16 and 31 g. of protein at one, six and twenty-four hours respectively.

Twenty-four hours after the infusions, 30 per cent of the administered dextran was present in the plasma while 60 per cent had been excreted in the urine. It is probable that a certain amount of the dextran unaccounted for (10 per cent of that infused) was present in the extracellular space, since, in other studies, dextran has been detected in the lymph shortly after its intravenous infusion. A small amount of dextran may also be excreted into the gastrointestinal tract. B. Aberg ("Some Experiments on Partly Hydrolysed Bacterial Dextran," *A. B. Bennel and Co., Stockholm (1952)*) reports that analyses of gastric juice samples from patients who received dextran intravenously showed a rising carbohydrate content which may be dextran or dextran degradation products. No dextran as such is found in the feces. However, E. J. Hehre and T. W. Sery (*J. Bact.* **63,** *424 (1952)*) have demonstrated that certain of the gram negative bacteria normally present in the feces contain an enzyme capable of breaking down dextran. I. Gray, P. K. Siiteri, and E. J. Pulaski (*Proc. Soc. Exp. Biol. Med.* **77,** *626 (1951)*) followed the excretion of dextran into the stomach, duodenum and remaining small bowel of 3 anesthetized dogs during the twenty-four-hour period following intravenous infusion of 200 ml. of a 6 per cent dextran solution. Less than 0.1 per cent of the infused dextran was found in any one of the three regions studied. Similarly, N. Burson and W. L. Bloom (*Am. J. Med.* **11,** *618 (1951)*) found only insignificant amounts of dextran in the gastrointestinal tract of patients following dextran infusions.

It has been suggested that the dextran which is not excreted in the urine will be slowly metabolized since only very limited quantities of dextran can be detected in the organs of animals given dextran intravenously.

To gain more direct information as to the possible metabolism of dextran, Gray and co-workers also studied the dextrose: nitrogen (D:N) ratio in the urine of phlorhizinized starved dogs given dextran intravenously to determine the possible *in vivo* conversion of dextran to glucose. Mongrel dogs of both sexes were starved except for water. After three days, daily injections of 1 g. of phlorhizin suspended in 10 cc. of olive oil were begun and continued for the duration of the experiment. When the D:N ratio became constant, usually after four to five days, 200 cc. of a 6 per cent dextran solution in isotonic saline were infused intravenously (rate not stated), and the studies were continued for three days. In each instance, there was a marked increase in the D:N ratio beyond the limits for the control period. For example, in one dog the average D:N ratio during the preinfusion period was 2.26 (range 1.70 to 2.56) and this rose to 3.66, twenty-four to forty-eight hours after the

infusion. The authors concluded that the change in the D:N ratio indicates the breakdown of dextran to dextrose. This was substantiated in part when I. Gray and G. P. Highland (*Annual Report of the Surgical Research Unit, Brooke Army Hospital, Fort Sam Houston, Texas, p. 15, (1952)*) later found in similar experiments, using C^{14}-labeled dextran, that a portion of the increased glucose excreted following dextran infusion was radioactive.

Gray and Highland also carried out more detailed metabolic studies. C^{14}-labeled dextran (0.2 ml. of a 6 per cent solution) was injected into the tail vein of white mice of either sex weighing 20 to 25 g. This corresponds to an infusion of approximately 700 ml. into a 70 kg. man. Changes in radioactivity of the total carcass and of various carcass fractions were measured over a period of days. It was observed that the metabolic half-life (calculated after the initial rapid urinary loss) of the carbon of dextran is 6.1 days. Activity in the carcass amino acid fraction increased rapidly in the first two days after infusion and then decreased rapidly for the next few days. After the fifth day the level was low and decreased very slowly. Incorporation of the C^{14} into the carcass carbohydrate fraction was also very rapid, reaching a peak on the first day. Then, as in the case of amino acids, the radioactivity fell sharply for a few days, leveling off after the fifth day. The uptake of C^{14} in the carcass fat was considerably slower than in either the carbohydrate or amino acid fractions. The incorporation of C^{14} in fat reached a peak on about the fifth day and then slowly declined. By the twelfth day the specific activity in each of these fractions was very similar. These data are presented as indicating that dextran is assimilated and utilized by the body and quickly converted into the substances normally found in the animal. Further evidence that dextran probably is metabolized, at least in part, was presented by W. H. Cargill and H. D. Brunner (*Drug Trade News* **26,** *46 (1951)*), who found C^{14}-labeled carbon dioxide in the expired air of mice infused with C^{14}-labeled dextran.

Relatively little information is available regarding the metabolism of dextran in man. B. Hellman (*National Research Council Report, Oct. 1951*) observed that over 90 per cent of C^{14}-labeled dextran infused into man was eliminated in ten days, 64 per cent in the urine and 26 per cent in the expired air as carbon dioxide.

Polyvinyl pyrrolidone (P.V.P.) is another apparently useful plasma expander. It is a synthetic, water-soluble macromolecular polymer which was effectively administered to large numbers of battle casualties in Germany during World War II for the treatment of traumatic shock. P.V.P. dissolved in physiologic saline in a concentration of 3.5 per cent is isotonic and iso-oncotic with plasma. As in the case of dextran, about 40 to 60 per cent of the presently available P.V.P. is excreted in the urine during the first two or three days after its infusion. No significant quantities are excreted into the gastrointestinal tract.

Some specific information about the fate of the P.V.P. not excreted has recently been obtained by H. A. Ravin, A. M. Seligman, and J. Fine (*New Engl. J. Med.* **247,** *921 (1952)*), utilizing radioactive tracer technics. P.V.P. was labeled with either I^{131} or C^{14}. The iodine labeling was interpreted as consistent with the addition of iodine to a single terminal double bond in each molecule of P.V.P. The C^{14}-tagged P.V.P. was prepared from radioactive acetylene and the carbon atoms of the polyvinyl chain were thereby labeled.

After the rapid infusion of I^{131}-P.V.P. into dogs anesthetized lightly with nembutal, the radioactivity in the plasma fell rapidly during the first one or two hours and then decreased more slowly. After four to six hours, the disappearance curve approached a straight line with a shallow slope. Forty to 80 per cent of the injected P.V.P. was excreted in the urine within the first forty-eight

hours after injection. Both the amount of P.V.P. remaining in the circulation during the initial postinfusion period and that excreted in the urine could be correlated with the average molecular weight of the P.V.P. preparation used, the smaller molecular weight fractions leaving the plasma and appearing in the urine first. It appears that the particles of P.V.P. excreted by the kidney are of a molecular weight less than 40,000. In dogs with thoracic duct fistulas, P.V.P. appeared in the lymph very quickly after infusion at a rate also directly related to the molecular size of the infused preparation. Thus, equilibrium between the plasma and lymph of P.V.P. with a molecular weight of 20,000 or less was established within an hour.

Similar results in regard to plasma disappearance and urinary excretion were observed with C^{14}-labeled P.V.P. infused into dogs, rats and patients. A small amount of P.V.P. (0.5 per cent) appeared in the feces in the human subjects and dogs in the first twenty-four hours following infusion. Thereafter fecal excretion was about 0.01 per cent per day of the infused P.V.P. By a biliary fistula technic, it was demonstrated that in the dog the fecal excretion of P.V.P. is entirely of biliary origin. No significant radioactivity was found in the expired air of human subjects given a purified preparation of C^{14}-labeled P.V.P. It was concluded from this that there is no significant metabolic degradation of P.V.P.

Analyses of P.V.P. in the tissues of rats, rabbits and moribund patients given C^{14}-P.V.P. intravenously were performed. The distribution of retained C^{14}-P.V.P. followed a similar pattern in the three species. The largest fraction of retained P.V.P. was in the skeletal muscle, skin and subcutaneous tissue. In terms of relative tissue concentration of P.V.P., skeletal muscle, skin and subcutaneous tissue were lowest, while the organs of the reticulo-endothelial system (liver, spleen, bone marrow and lymph nodes) were highest. The P.V.P. retained in the skin, subcutaneous tissue and skeletal muscles decreased progressively after the infusion of P.V.P. The uptake of P.V.P. by the reticulo-endothelial system was largely completed within two weeks following its administration and the net turnover of P.V.P. sequestered within the reticulo-endothelial system was very slow. After its initial rapid urinary excretion, P.V.P. was excreted slowly in the urine for as long as a year after its intravenous infusion. When preparations of P.V.P. of different molecular weight were infused, the over-all retention of P.V.P. could be correlated with molecular weight, the higher molecular weight fractions being retained for the longer periods of time. The minimal molecular weight for P.V.P. retained by the reticulo-endothelial system appeared to be around 117,000. Ravin, Seligman and Fine observed no deleterious effects in their animals attributable to the long-term retention of P.V.P., but more information in this regard is needed for human subjects.

A PROTEIN FACTOR ESSENTIAL FOR LACTATION

Failure of adequate lactation in the postparturition period has long been thought to be due partly to possible generic factors and partly to either hormonal imbalances, or failure of the breast tissues to respond to proper hormonal stimulation. Evidence has been presented by M. O. Schultze (*J. Nutrition* **41,** *103 (1950)*; **42,** *587 (1950)*) that in addition certain dietary deficiencies may be of prime importance in lactation failure. This work has recently been extended to show that the diet of the "grandmother" animals can also influence the lactation performance of the subsequent

generation, and the survival of following generations (Schultze, *Ibid.* **49,** *231, 245 (1953)*).

The animals used were the first filial and following generations of rats raised since weaning on a 24 per cent soya bean protein diet. Survivors from each generation were raised to maturity on the same ration and females were bred when 10 weeks old with males maintained on this diet. Litters were weaned at 21 days. Rats have been maintained on this regimen for ten successive generations.

The rations used contained synthetic vitamin A acetate instead of the fish liver concentrate used previously. They were adequately supplemented with all known vitamins, including biotin. Soya bean protein samples were used as the basis of the ration during the three years of the study period. These frequently differed physically and chemically in certain respects and in some cases had certain pronounced differences in their nutritional properties. These differences are not described fully in the paper.

There was a relatively low or "normal" mortality in the first litter of young from rats maintained from 21 days of age on purified soya protein, the mothers of which had been maintained on unpurified soya bean sodium proteinate. However, mother rats on the purified diet, whose mothers were also maintained on the same highly purified soya bean protein preparation, had extremely high preweaning mortality in their first litter young. Data are not supplied relative to mothers in further generations of animals receiving the purified soya fractions. The purified soya bean protein in the maternal diet also caused a progressive decrease of survival in successive litters borne by a mother rat. The first-litter mortality rate might approximate 18 per cent, but the second or third litters would have preweaning mortality rates of 50 per cent or more, in many instances. In some cases deaths in subsequent litters rose as high as 93 per cent. Supplementary vitamin B_{12} in the diet for as long as fifty-nine days prepartum had no demonstrable curative action on the deficiency syndrome, once it was established, in the mother animal.

In those rats whose litters showed nearly 100 per cent mortality because of the dietary deficiency in the mother, the feeding of soya bean oil meal, instead of the purified soya bean protein in the ration, had a pronounced curative effect, even if the material was fed only from the time of parturition through lactation. Certain of the soya bean sodium proteinate fractions were apparently deficient in threonine, for mothers receiving the material had severe weight loss, particularly during the early stages of lactation, and the young grew very slowly until the diet was supplemented with threonine. There was no evidence, however, that threonine per se was the factor responsible for the high litter mortality rate.

The stomachs of the young rats dying during lactation phases contained extremely small amounts of milk. For that reason, half of the young from mothers on purified soya bean protein diets were transferred to mothers maintained on complete diets. Young animals whose foster mothers were in the latter group had a greatly reduced mortality rate. Foster young nursed by mothers on the deficient diet had a mortality rate as high as that of their own offspring. The data suggest, therefore, that animals fed the soya bean ration of purified type are unable to produce milk either of adequate quality or of sufficient quantity to permit survival of the litters. It is emphasized, however, that variability has been encountered in the ability of the commercial preparation of the soya bean protein to establish this dietary deficiency, that is not correlated clearly with the technic used for purification.

In an attempt to cure the deficiency in lactation, various dietary supplements were tested. After the weaning of the second litter of mothers on purified soya bean protein ration, with a high incidence of prewean-

ing mortality, the diet was supplemented with 2 per cent or 10 per cent of a water-soluble concentrate prepared from cereals. The preparation was found to be devoid of curative action on the lactation failure.

Because of the demonstration that a deficiency in folacin may increase the preweaning mortality of young rats, presumably through poor lactation in the mother, folacin (0.2 mg. per kilogram of body weight) was added to the soya bean protein diet. This also failed to relieve the high lactation failure and mortality. The urine of rats on the deficient diet, whether supplemented with grass juice concentrate or folacin, demonstrated a great increase in the output of citrovorum factor. Therefore, the lactation failure is probably not a result of deficiency in citrovorum factor per se.

Substitution of vitamin-free casein in place of the soya bean protein preparations in animals in which the litter mortality had increased to more than 90 per cent effected a substantial reduction in death rates of the young animals to 25 or 35 per cent. The substitution of a crude animal protein for the soya bean preparation reduced the preweaning mortality of litters from ranges of 80 to 90 per cent to approximately 7 per cent.

Because of the demonstration that orotic acid is a possible galactogogue, studies were carried out on rats receiving the purified soya bean protein diets supplemented with this agent. Mortality rates in the litters of animals so supplemented fell from over 90 per cent to 56 per cent. Attempts to demonstrate that prefeeding with orotic acid had a prophylactic value with regard to the development of the lactation deficiency were not conclusive.

Keane's factor in wheat germ oil and also in certain natural fats necessary for adequate nourishment of the preweanling rat (K. W. Keane, E. M. Cohn, and B. C. Johnson, *J. Nutrition* **45,** *275 (1951)*) was not present in a ration well supplemented with vitamin-free casein. Such casein apparently greatly ameliorated the deficiency in the present study. W. Nakahara, F. Inukai, S. Ugami, and Y. Nagata (*Chem. Abstr.* **41,** *6317 (1947)*) discovered two lactation factors for rats which apparently are comparable to anthranilic acid or adenylthiomethyl pentose. Nakahara's diets were quite different, however, from those used in the present study, and similarities between his lactation factors and those in the soya bean protein diet are unlikely. The lactation principle observed by M. Piccioni, A. Rabbi, and G. Moruzzi (*Science* **113,** *179 (1951)*) in a diet containing largely cereal grains and rather thoroughly washed casein, may be comparable to that noted in the diet in the series of experiments discussed in this review.

It is apparent from this study that the failure of lactation in animals on these diets is not a result of a deficiency of folacin, citrovorum factor, orotic acid, or of any of the recognized vitamins, when supplied in the usual amounts. Because of the fact that feeding of crude animal protein preparations completely cured the lactation deficiency, the agent or agents responsible for it conceivably represent a new principle closely associated with certain animal proteins.

NOTES

Thyroid Activity and Lipogenesis

The old question of the relation of thyroid gland activity to fat deposition has been reinvestigated in rats by B. Kennelly and L. A. Maynard (*J. Nutrition* **49,** *599* (*1953*)). Two highly purified rations were employed, one extremely low in fat, the other of moderate fat content. These rations were supplemented either with desiccated thyroid powder or with thiouracil. Suitable control rats were fed the two diets without supplementation. One of the unique features of this experiment is that animals in each experimental group were fed exactly 2000 calories, the time required for the consumption of this amount of food being taken as an index of the rate of food consumption. Rectal temperature and oxygen consumption were measured and the carcasses were analyzed for water and lipids. The latter were determined as neutral fats, cerebrosides, free cholesterol, cholesterol esters, cephalin, lecithin and sphingomyelin.

The addition of thyroid powder to the low fat diet raised the animals' body temperature, increased oxygen consumption and decreased the weight gained during the consumption of 2000 calories of diet. The addition of thyroid to the moderate fat diet had no significant effect. At both fat levels the addition of thiouracil lowered body temperature as well as oxygen consumption. These animals also required longer to consume the full 2000 calories, although this effect of thiouracil was significant only with the diet of moderate fat content. Neither the fat content of the diet nor the addition of thiouracil or thyroid powder had any significant effect on the carcass content of "essential" lipids (cerebrosides, cholesterol and its esters and the phospholipids). On the other hand, the neutral fat content was drastically influenced. At both fat levels the addition of thiouracil significantly increased the neutral fat content of the carcass. On the low fat diet the addition of thyroid powder decreased the neutral fat level. On the high fat diet thyroid addition somewhat lowered neutral fat, but the effect was not significant.

Ascorbic Acid and Cholesterol Synthesis

The possible relationship of ascorbic acid to adrenocortical function has been repeatedly discussed (*Nutrition Reviews* **3,** *37* (*1945*); **8,** *52* (*1952*)). It has been interesting to speculate that ascorbic acid is essential for the synthesis of adrenal steroids. However, careful study of the effects of experimental scurvy on the excretion of urinary 17-ketosteroids has not given support for this hypothesis. Severely scorbutic monkeys excrete 17-ketosteroids at a rate comparable to control monkeys (*Ibid.* **11,** *150* (*1953*)). Earlier experiments with guinea pigs had indicated that the excretion of 17-ketosteroids was slightly reduced in animals with severe scurvy (S. Banerjee and C. Deb, *J. Biol. Chem.* **194,** *575* (*1952*)).

A study of the relationship of ascorbic acid to steroid synthesis has been undertaken by R. R. Becker *et al.* (*J. Am. Chem. Soc.* **75,** *2020* (*1953*)). These workers studied the effects of ascorbic acid deficiency in guinea pigs on the incorporation of 1-C^{14} acetate into liver and adrenal cholesterol. Ascorbic acid-deficient guinea pigs and controls receiving a cholesterol-free chow diet were given three injections of labeled sodium acetate (1 mg., 2.68×10^7 counts per minute per milligram) at nine-hour intervals. The animals were killed four hours after the last injection and liver and adrenal cholesterol was isolated and purified There were 3 animals per group.

The specific activities of adrenal and liver

cholesterol respectively were: normal, fed ad libitum, 100, 80; mild scurvy, 170, 75 (pair-fed controls, 150, 80); severe scurvy, 600, 145 (pair-fed controls 195, 90). Thus it is obvious that the ascorbic acid-deficient guinea pigs incorporated much more acetate into cholesterol than did controls. These results certainly indicate that ascorbic acid deficiency in the guinea pig does not impair the synthesis of the steroid nucleus. The authors did not attempt to interpret the increase in acetate incorporation into cholesterol which accompanied scurvy. Extension of these results will be of interest.

Globin Metabolism

Modified human globin derived from human red blood cells has been proposed as a plasma volume expander and also as a source of protein for intravenous administration. Were globin to be a good plasma expander it should have, in addition to other physical properties, a relatively long half-life and should not be suitable, for this reason, as a source of parenteral protein nutrition. On the contrary, were it to have a relatively short half-life, that is, be broken down rapidly, it would more likely be satisfactory for parenteral protein nutrition but less able to maintain an expanded plasma volume. Thus, the two uses seem to be mutually exclusive.

S. A. Berson *et al.* (*J. Clin. Invest.* **32,** *22 (1953)*) have used globin labeled with radioactive iodine intravenously in human subjects to trace the distribution and fate of globin and to measure its effect on blood volume. They compared globin to intravenously administered serum albumin, likewise labeled with I^{131}. Intravenously administered globin was clearly demonstrated to disappear from the blood stream much more rapidly than albumin. This should make it a far poorer expander than albumin and measurements of plasma volume substantiated this, since they indicated only slight changes in plasma volume after globin administration. Because there is an increase in radioactivity over the liver after globin administration which gradually decreased during the period of an hour, because of the rapid disappearance of globin from plasma, and finally because of a progressive increase of total excretion of nonprotein bound radioactive iodine in the urine the authors believed that the intravenously administered globin was relatively rapidly metabolized, presumably in the liver.

These studies were done in 2 individuals and the authors felt justified in concluding that the results indicated that globin would not be a good plasma expander. It may be, as noted above, that globin will be a satisfactory means of furnishing protein for parenteral administration, if it proves to be harmless.

Present Knowledge in Nutrition

"Present Knowledge in Nutrition," a new Nutrition Foundation publication, has just come off the press. This 122-page booklet is based on material which appeared originally in *Nutrition Reviews*. Before being brought together for "Present Knowledge in Nutrition," this source material was revised in the light of current research. In the first chapter the present knowledge of calories is discussed in some detail. Subsequent chapters deal with the present status of the carbohydrates, fats, and proteins, with parenteral nutrition, mineral elements, the vitamins, vitamin-enzyme relationships, methyl groups, and the relation of nutrition to dental caries. The student of nutrition and the professional worker in the field of nutrition and health education will find this carefully prepared digest a reliable guide to nutrition research and to current nutrition practice. Copies are available from The Nutrition Foundation, Inc., Chrysler Building, New York 17, New York. Price: $2.00 per copy.